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SOVIET COMMENTARY ON US MICROBIOLOGICAL RESEARCH

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[Following is a translation of an article by Professor G. F. Gauze in the Russian-language periodical Vestnik Akademii Meditsinskikh Nauk SSSR (Journal of the Academy of Medical Sciences USSR), Moscow, No. 3, 1960, pages 78-82.]

The invitation extended me by the University of Chicago to participate in the Jubilee Darwinian Session and to lecture at Yale and Cornell on the theme "Ways of Finding New Antibiotics" provided me with the opportunity to visit America in November-December 1959 and in the course of a month to acquaint myself with a number of scientific centers in Washington, New York, New Haven and Ithaca which are conducting research in the field of microbiology and the study of antibiotics.

In the beginning of November 1959 the seventh annual symposium on antibiotics, organized by the journal "Antibiotics and Chemotherapy," was held in Washington. At this symposium about 300 reports from 23 countries, including Czechoslovakia and Poland, were read. The organizing committee for the conference selected about 150 reports to be read at sectional meetings; the remaining reports were not heard, but will be published in the periodical literature. The following sections made up the symposium: clinical application of antibiotics, including the observation of side effects; the use of antibiotics in pediatrics; the problem of resistant strains of staphylococcus. In addition, there were sections on new antibiotics, antifungous and anticancer antibiotics. Special sessions were devoted to methods of determining the sensitivity of microorganisms to antibiotics.

Among the new antibiotics described for the first time in 1959, the following deserve mention. Aspartocin is a new antibiotic-polypeptide, formed by a special variety of Actinomyces. It resembles amphomycin, but is easily distinguished from it on paper chromograms. Aspartocin is made up of aspartic acid, glycocoll, proline, valine, and a fraction of fatty acids. It is interesting to note that phosphates inhibit the biosynthesis of this antibiotic. Aspartocin administered subcutaneously or intravenously possesses a chemotherapeutic action specific for infections caused by pathogenic cocci. Given orally, aspartocin has no effect.

Fervenulin -- a new antibiotic formed from Actinomyces; it is a yellow, crystalline substance with the empirical formula $C_7H_7N_5O_2$. It exhibits a slight chemotherapeutic effect.

Streptozotocin -- a new antibiotic from a culture of Actinomyces with a broad-spectrum action, it has the empirical formula $C_{14}H_{27}N_5O_{12}$ and contains in its molecule the nitrosomethylamide group. This antibiotic exhibits a pronounced chemotherapeutic effect in experiments on animals with respect to pathogenic cocci, and also to bacteria of the typhoid group and Proteus. Bacteria resistant to other antibiotics are sensitive to streptozotocin. However, upon contact with streptozotocin, staphylococci and Proteus quite readily exhibit resistant forms; the speed of this process belongs to the "streptomycin" type.

Ryphomycin is a complex of a number of similar antibiotics from a culture of a new strain of Actinomyces. Toxicity is low and it exhibits chemotherapeutic activity in respect to pathogenic cocci and mycobacteria. Ryphomycin has been used in the clinic for staphylococcus infections, being administered intramuscularly. Results were positive.

Paromomycin is a broad-spectrum drug and exhibits pronounced chemotherapeutic activity in the case of cocci, gram-negative bacteria and intestinal amoeba. A clinical laboratory study of this antibiotic in more than 1,000 patients showed that it assimilates well when administered orally, and combines low toxicity with high antibacterial and antiamoebic activity.

Summing up the results of this section of the symposium's work, it can be concluded that the search for new, effective antibacterial antibiotics is continuing to develop successfully, and that 1959 saw the discovery of a number of new, effective medicinal preparations. In evaluating the results of this work it should be noted that it is the result of a year's work by more than 20 scientific institutes in the US conducting research in the creation of new antibiotics.

Among the other antibacterial antibiotics ristocetin received favorable notice; the crystalline sulfate of this drug is administered by intravenous infusion in serious staphylococcus infections in infants and juveniles. Another of these antibiotics was vankomycin. Kanamycin continues to be used with success in the treatment of peritonitis and various infections caused by pathogenic cocci and gram-negative bacteria.

The outstanding success of the antifungous antibiotic griseofulvin was demonstrated at one session, where seven reports were heard on the clinical testing of this preparation. Treatment of trichophytosis and certain other dermatomycoses by griseofulvin, administered orally, proved very effective. In doses of about 1 gram a day this antibiotic exhibited a systemic effect. It contains keratin and makes the skin a completely unsuitable medium for the growth of dermatophytes belonging to the genera Trichophyton and Microsporon.

Among the new anticancer antibiotics is streptonigrin, formed by a new species of Actinomyces. Crystals of streptonigrin appear as brown rectangular flakes, with the empirical formula $C_{24}H_{20}O_8N_4$, and have the properties of quinones. Streptonigrin exhibits an antibacterial effect and markedly inhibits the growth of adenocarcinoma and strains of human cancer transplanted in rats. With respect to Crocker's sarcoma and leukemia in mice, this preparation exhibited only moderate effect.

Diazomycin is formed by Actinomyces and belongs to the group of aliphatic diazoketones. This antibiotic was obtained in crystalline form; it exhibited a strong inhibiting effect on Crocker's sarcoma and adenocarcinoma in experiments on animals.

Significant new results were obtained in 1959 in the study of antibiotics of the tetracycline group. In cultures of Actinomyces, forming tetracycline, a mutant was observed which formed chiefly dimethylchlortetracycline (DMCT). This preparation possesses considerably greater stability and activity in comparison with tetracycline, and therefore exhibits a superior medicinal effect in small doses. As a result, this preparation produces fewer side effects than tetracycline.

Considerable attention was devoted in 1959 to obtaining new variants of penicillin through synthesis. In this case the "nucleus" of penicillin (so-called penicillic acid) is prepared by biosynthesis in mold cultures, subsequent chemical combination of the side chains converting it into new types of penicillin. In 1959, one US institute for antibiotics obtained over 500 new synthetic penicillins for the purpose of discovering among them broad-spectrum types. Actively being investigated is the problem of whether the addition of new side chains to penicillin can lead to the creation of substances active against viruses and tumors.

Besides the visit to the antibiotic division of the US Department of Health in Washington, headed by G. Welch and D. Grove, who organize the annual symposiums on antibiotics, of considerable interest was the work of the National Center for the Chemotherapy of Cancer in Washington. This center, directed by S. Sessoms and R. Coghill, is part of the system of the national institutes of health under the US Department of Health.

The search for new products of the metabolism of microorganisms, possessing antitumor activity, is organized in the following manner. The raw material for the tests, i.e., the liquid culture media of various microorganisms and their concentrates, are prepared by the scientific-research institutes of pharmaceutical firms, and are tested for antitumor activity either in the same institutes or in a special test center in Rye, New York. The test center is located in a special building constructed in 1958 and is well equipped with the necessary apparatus. The work of this center, as well as the work of the pharmaceutical institutes, in the search for antibiotics against cancer is financed by the US Government through the National Center for Cancer Chemotherapy in Washington.

In the course of this work, the Antibiotic Institute of the Pfeizer firm in 1959 tested about 10,000 new liquid culture media and antibiotic raw materials for their activity against tumors. About 20 of these substances proved active, and their further study is planned. About 100 persons took part in this work. In addition, the expediency of using various new models for selecting antitumor substances is being studied, in particular human tumors transplanted in conditioned animals. Similar investigations are being conducted in the antibiotic institutes of the Bristol, Upjohn, Parke Davis, Abbot and other pharmaceutical firms. In the Merk institute, the US Government is mainly subsidizing work of a theoretical nature connected with the study of the biochemical differences between normal and tumor cells, as a basis for developing an effective chemotherapy of cancer.

During my stay in Washington, the director of the National Institute of Health, Mr. Shannon, and his assistant, Mr. Smadel, offered me the opportunity to visit a number of laboratories of this institute. Of considerable interest was the work of A. Goldin and his co-workers in the laboratory of chemical pharmacology. This work is devoted to the analysis of the combined action of various antitumor preparations in experimental leukemia in mice (strain 1210). Best results were obtained with the use of ametopterin (diamino-6-pteridyl-methyl-methylamino-benzoil-glutamic acid), which is put out by the Lederle firm under the name Metotrexate. This preparation is an analog of folic acid, which plays an important role in the biosynthesis of nucleic acids in cells. Ametopterin is currently being used with success in clinics for the treatment of acute leukocytosis and choriocarcinoma.

The laboratory of the Institute of Allergies and Infectious Diseases, headed by G. Eagle (Igl), is studying methods for the initial selection of antitumor preparations. Being studied for this purpose is parallelism in the effect of a large number of active preparations on various tumors in animals, on the growth of tumor cells in tissue cultures, and on the growth of various cultures of microorganisms. As it turned out, the use of cultures of three different microorganisms (infusoria of tetrachymen, lactobacillus and neurospore molds) in combination with samples in tissue cultures permits early recognition of active antitumor preparations in 97% of cases.

From the 24th through the 28th of November 1959 at the University of Chicago, a scientific session was held in honor of the 100th anniversary of the publication of Charles Darwin's famous book on the origin of the species through natural selection. Participating in the session were 2,500 scientists from 27 countries, of which number 50 specialists had been invited to present papers on general problems of biology and medicine. Notable among these reports was one by Professor Gang (of Johns Hopkins University,

Baltimore), entitled "Pavlov and Darwin." The report noted that Pavlov and the genius Darwin to a large extent assisted in freeing science of various prejudices regarding evolution and the working of the brain.

The author of these lines read a paper on the theme, "Darwinism and Certain Problems in the Study of Analogs of Cancer Cells and Microbes," which had appeared in the Journal of the Academy of Medical Sciences USSR in 1959 (No. 2, pp. 49-53).

In connection with the jubilee session, the University of Chicago organized a series of round-table discussions. Usually, six or seven scientists took part in these discussions, which were held on the stage of the university theater before an audience of several thousand people. The discussions were carefully prepared beforehand by members of the discussion group. I was invited to take part in a discussion on the origin of life, presided over by the well-known American astronomer Harlow Shapley (Shepli). In general, the participants came to the same conclusions as did the international symposium on the problem of the origin of life on earth, conducted in 1957 by the Academy of Sciences USSR in Moscow. In this connection, the concord between Soviet and American scientists in the discussion of this important question was given favorable notice by the American press.

Interesting work is being conducted at the University of Chicago in the field of molecular biology by the department of biochemistry, headed by E. Evans. With the aid of modern methods of investigation they have obtained quite convincing data on the dynamics of the process of injection of desoxyribonucleic acid into a bacterial cell with a bacteriophage, accomplished by discrete changes in the size of the phage's head, which represents a unique "syringe." In 1959 the University of Chicago announced a special symposium devoted to problems of molecular biology.

Not far from Chicago is a large institute which is conducting work on the search for new antibiotics; its directors invited me to visit their laboratory. A characteristic feature of the work of this institute, as well as that of a number of similar institutes in the US, is the wide application of the chromatography of liquid culture media as a method of discovering new antibiotics in the earliest possible stages of investigation. Twelve standard systems of solvents are employed which facilitate recognition of antibiotics already known and permit effort to be concentrated on a more detailed study of new chemical substances.

The Institute for the Discovery of New Antibiotics, Academy of Medical Sciences USSR, has in the past few years developed another method of solving this same problem, based on a detailed classification of producents [sic] and the spectral analysis of their antibacterial effect. Apparently, microbiological as well as chemical principles of research are producing similar results

in practice. Quite interesting is the parallel application of these different methods of investigation in research to discover their advantages and shortcomings.

At Yale University, located not far from New York, the institute of pharmacology, headed by Arnold Welch, is highly interesting. This institute is conducting intensive work on the search for and the study of the mechanism of action of new anticancer preparations. An especially detailed study is being made of the mechanism of the carcinostatic action of asauracyl and its riboside, belonging to the group of antimetabolytes of pyrimidine nucleotides. Recently at this institute, Glen Fisher achieved considerable success in cultivating cells of mouse leukemia in test tubes. One of the strains of the leukemia cells multiplied quite intensively, and by isolating it from the other cells Fisher succeeded in obtaining a culture which was homogeneous in the genetic respect. Here, the entire procedure did not differ essentially from ordinary microbiological methods. Mutants of the leukemia cells, resistant in the test tube to the anticancer preparation amethopterin, caused leukemia in mice which did not respond to treatment with amethopterin.

In New York I had the opportunity to acquaint myself with the work of the Rockefeller Institute for Medical Studies, one of the most interesting and best equipped institutions in the US in the field of experimental medicine. The chemistry department, under Mr. Craig, is studying the chemical structure of antibiotics of a polypeptide character -- subtilin and bacitracin. Craig acquainted me with a new type of counterflow diffusion apparatus, recently developed in his laboratory. This apparatus is considerably more compact and convenient to use than the previous model.

In the same department, Speckman, Stein and Moore recently designed a very interesting apparatus for the automatic analysis of amino acids, which undoubtedly will be widely used in biochemical and medical laboratories. US industry is currently manufacturing this device, and the first models have already been installed in a number of laboratories. The operating principle of this device is based on the quantitative determination of the content of different amino acids by automatically recording the coloration of ninhydrin in the eluate from an ion-exchange column. A buffer solution, containing no air, is forced by a special constant-speed pump into a chromatographic column containing a sulfopolystyrene resin. The eluate in the capillary flow meets the ninhydrin reagent, which is fed in by a second pump. To make the color show up, the mixture of the ninhydrin reagent and the eluate is passed through a spiral capillary made of teflon, immersed in a tank of boiling water. The absorption of the effluent solution at 570 and 440 mμ is constantly measured and automatically recorded, indicating the qualitative and quantitative content of the various amino acids. A complete analysis of the protein hydrolysate is provided by this apparatus in less than 24 hours.

In one of the laboratories of the Rockefeller Institute I became acquainted with the work of the biochemist Bully, author of the well-known book on antimetabolytes. In a number of his investigations Bully noted the special ability of spontaneous tumors in animals to synthesize vitamin B_{12}, which he attempted to employ in creating antimetabolytes, selectively inhibitive for tumor cells.

In 1939, in the laboratories of the microbiologist Dubos and the chemist Hotchkiss, tyrothricin was discovered -- the first antibiotic exhibiting a medicinal effect. In connection with this, twenty years after the discovery, Dubos read a special report at the symposium on antibiotics in 1959. Hotchkiss currently is conducting extensive research on the transforming effect of desoxyribonucleic acid on bacteria. In his laboratory the various steps in the process of transformation are being analyzed in detail: first, the readiness of cells to transform or to develop competence, both of which are connected with the composition of the culture medium and reach a maximum at the end of the logarithmic phase of bacterial growth; second, the fixation of desoxyribonucleic acid in cells of competent bacteria, which proceeds according to the law of reverse chemical reaction; third, the process of manifestation (or genetic expremia [sic]) in the cell of new inherited characteristics, induced by desoxyribonucleic acid; and fourth, the reproduction of inherited cell changes in new generations. The material for these investigations are primarily the changes in capsule properties and drug fastness in various cultures of pneumococci.

In New York I also had the opportunity to visit the Sloan-Kettering Institute for the Study of Cancer. This institute is conducting research in various directions, including the biochemistry and chemotherapy of cancer. The chemistry department of this institute, under Mr. Brown, is conducting a detailed study of desoxyribonucleic acid extracted from tumor cells; wide use is made of various modern physico-chemical methods of investigation. At the same institute Doris Hutchison is making a detailed study of the biochemical principles involved in the development of the resistance of tumor cells to anticancer preparations, particularly to mercaptopurine. For model experiments wide use is made of cultures of various microorganisms, including streptococci. It was established that various biochemical mechanisms underlie the resistance of different strains to mercaptopurine.

After familiarizing myself with the scientific institutions of New York, I was invited to lecture and to acquaint myself with the work of Cornell University in Ithaca, in the northern part of New York State. This university possesses a well-equipped laboratory conducting work in the field of general microbiology. Of considerable interest is the work being done by Mr. Alexander and his co-workers to discover and obtain certain antibiotic substances directly from the soil. In particular, in certain tropical soils

substances were discovered which inhibited the growth of fungi, and it was shown that the formation of these substances was closely related to the activity of soil microorganisms. Research is currently being conducted to extract from soil certain of these substances in ion-exchange resins.

In summing up the results, it can be stated that work in the US on the search for new, effective antibacterial antibiotics is proceeding along a wide front. About 20 scientific research institutes are taking part in this work, and they are continuing to discover new, effective medicinal preparations, as can be attested to by the annual symposiums on antibiotics in Washington.

The further improvement of laboratory methods of investigation is of interest, in particular the apparatus for the automatic analysis of amino acids and Craig's new apparatus for counterflow diffusion.

All that is positive in US laboratory science can be realized in the USSR.

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